

PATENTS

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANTS: POPP ET AL -1 US  
SERIAL NO.: 10/059,774 EXAMINER: I. MARX  
FILED: JANUARY 30, 2002 GROUP: 1651  
TITLE: A PROCESS FOR THE ENZYMATIC PREPARATION OF  
ENANTIOPURE 1,3-DIOXOLAN-4-ONE AND 1,3-OXATHIOLAN-5-  
ONE DERIVATIVES

PETITION UNDER RULE 136(a) AND RULE 17(a)(1)

MAIL STOP: AFTER FINAL  
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S I R :

Applicant petitions the Commissioner of Patents and Trademarks to extend the time for response to the Office Action dated March 4, 2004 for one month from June 4, 2004 to JULY 4, 2004. A check in the amount of \$110.00, covering the fee for a one-month extension for a Large Entity is enclosed herewith. Any deficiency or overpayment should be charged or credited to deposit Account No. 03-2468.

Respectfully submitted,

Alfred POPP et al

COLLARD & ROE, P.C.  
1077 Northern Boulevard  
Roslyn, New York 11576  
(516) 365-9802

Allison C. Collard; Reg.No. 22,532  
Edward R. Freedman; Reg.No. 26,048  
William C. Collard, Reg.No. 38,411  
Attorneys for Applicants

Enclosure: Check in the amount of \$110.00

I hereby certify that this correspondence is being deposited with the U.S. Postal Service as first class mail in an envelope addressed to: MAIL STOP: Fee Amendment, Commissioner of Patents, U.S. PTO, P.O. Box 1450, Alexandria, VA 22313-1450, on July 6, 2004.

  
Ingrid Mittendorf

Equation 5

where X = oxygen or sulfur and

the radicals  $R^1$  and  $R^2$  are different and are selected independently of one another from the group consisting of H, substituted or unsubstituted  $C_6-C_{18}$ -aryl,  $C_3-C_{18}$ -heteroaryl,  $C_1-C_{18}$ -alkyl,  $C_2-C_{18}$ -alkenyl,  $C_2-C_{18}$ -alkynyl,  $C_6-C_{18}$ -aryl- $C_1-C_{18}$ -alkyl,  $C_3-C_{18}$ -heteroaryl- $C_1-C_{18}$ -alkyl,  $C_6-C_{18}$ -aryl- $C_2-C_{18}$ -alkenyl,  $C_3-C_{18}$ -heteroaryl- $C_2-C_{18}$ -alkenyl,  $C_1-C_{18}$ -alkoxy- $C_1-C_{18}$ -alkyl,  $C_1-C_{18}$ -alkoxy- $C_2-C_{18}$ -alkenyl,  $C_6-C_{18}$ -aryloxy- $C_1-C_{18}$ -alkyl,  $C_6-C_{18}$ -aryloxy- $C_2-C_{18}$ -alkenyl,  $C_3-C_8$ -cycloalkyl,  $C_3-C_8$ -cycloalkyl- $C_1-C_{18}$ -alkyl,  $C_3-C_8$ -cycloalkyl- $C_2-C_{18}$ -alkenyl, and  $CR^8R^9-O_n-(CO)_m-R^{10}$  and the radicals  $R^3$  and  $R^4$  are selected independently of one another from the group consisting of substituted or unsubstituted  $C_1-C_{18}$ -aryl,  $C_1-C_{18}$ -heteroaryl,  $C_1-C_{18}$ -alkyl,  $C_2-C_{18}$ -alkenyl,  $C_2-C_{18}$ -alkynyl,  $C_6-C_{18}$ -aryl- $C_1-C_{18}$ -alkyl,  $C_3-C_{18}$ -heteroaryl- $C_1-C_{18}$ -alkyl,  $C_6-C_{18}$ -aryl- $C_2-C_{18}$ -alkenyl,  $C_3-C_{18}$ -heteroaryl- $C_2-C_{18}$ -alkenyl,  $C_1-C_{18}$ -alkoxy- $C_1-C_{18}$ -alkyl,  $C_1-C_{18}$ -alkoxy- $C_2-C_{18}$ -alkenyl,  $C_6-C_{18}$ -aryloxy- $C_1-C_{18}$ -alkyl,  $C_6-C_{18}$ -aryloxy- $C_2-C_{18}$ -alkenyl,  $C_3-C_8$ -cycloalkyl,  $C_3-C_8$ -cycloalkyl- $C_1-C_{18}$ -alkyl, and  $C_3-C_8$ -cycloalkyl- $C_2-C_{18}$ -alkenyl or the radicals  $R^3$  and  $R^4$  form, together with the carbon to which they are bonded, an unsubstituted or substituted or a heteroatom-containing cycloalkylidene and Nu is  $OR^5$ ,  $SR^5$  or

NR<sup>6</sup>R<sup>7</sup>, where

the radicals R<sup>5</sup> are selected from the group consisting of H, substituted or unsubstituted C<sub>1</sub>-C<sub>18</sub>-alkyl, C<sub>2</sub>-C<sub>18</sub>-alkenyl, C<sub>2</sub>-C<sub>18</sub>-alkynyl, C<sub>6</sub>-C<sub>18</sub>-aryl-C<sub>1</sub>-C<sub>18</sub>-alkyl, C<sub>3</sub>-C<sub>18</sub>-heteroaryl-C<sub>1</sub>-C<sub>18</sub>-alkyl, C<sub>6</sub>-C<sub>18</sub>-aryl-C<sub>2</sub>-C<sub>18</sub>-alkenyl, and C<sub>3</sub>-C<sub>18</sub>-heteroaryl-C<sub>2</sub>-C<sub>18</sub>-alkenyl, and the radicals R<sup>6</sup> and R<sup>7</sup> are selected

independently of one another from the group consisting of H, substituted or unsubstituted C<sub>1</sub>-C<sub>18</sub>-alkyl, C<sub>2</sub>-C<sub>18</sub>-alkenyl, C<sub>2</sub>-C<sub>18</sub>-alkynyl, C<sub>6</sub>-C<sub>18</sub>-aryl, C<sub>3</sub>-C<sub>18</sub>-heteroaryl, C<sub>6</sub>-C<sub>18</sub>-aryl-C<sub>1</sub>-C<sub>18</sub>-alkyl, C<sub>3</sub>-C<sub>18</sub>-heteroaryl-C<sub>1</sub>-C<sub>18</sub>-alkyl, C<sub>6</sub>-C<sub>18</sub>-aryl-C<sub>2</sub>-C<sub>18</sub>-alkenyl, and C<sub>3</sub>-C<sub>18</sub>-heteroaryl-C<sub>2</sub>-C<sub>18</sub>-alkenyl,

and the radicals R<sup>8</sup> and R<sup>9</sup> are selected independently of one another from the group consisting of substituted or

unsubstituted C<sub>6</sub>-C<sub>18</sub>-aryl, C<sub>3</sub>-C<sub>18</sub>-heteroaryl, C<sub>1</sub>-C<sub>18</sub>-alkyl, C<sub>2</sub>-C<sub>18</sub>-alkenyl, C<sub>2</sub>-C<sub>18</sub>-alkynyl, C<sub>6</sub>-C<sub>18</sub>-aryl-C<sub>1</sub>-C<sub>18</sub>-alkyl, C<sub>3</sub>-C<sub>18</sub>-heteroaryl-C<sub>1</sub>-C<sub>18</sub>-alkyl, C<sub>6</sub>-C<sub>18</sub>-aryl-C<sub>2</sub>-C<sub>18</sub>-alkenyl, C<sub>3</sub>-C<sub>18</sub>-heteroaryl-C<sub>2</sub>-C<sub>18</sub>-alkenyl, C<sub>1</sub>-C<sub>18</sub>-alkoxy-C<sub>1</sub>-C<sub>18</sub>-alkyl, C<sub>1</sub>-C<sub>18</sub>-alkoxy-C<sub>2</sub>-C<sub>18</sub>-alkenyl, C<sub>6</sub>-C<sub>18</sub>-aryloxy-C<sub>1</sub>-C<sub>18</sub>-alkyl, C<sub>6</sub>-C<sub>18</sub>-aryloxy-C<sub>2</sub>-C<sub>18</sub>-alkenyl, C<sub>3</sub>-C<sub>8</sub>-cycloalkyl, C<sub>3</sub>-C<sub>8</sub>-cycloalkyl-C<sub>1</sub>-C<sub>18</sub>-alkyl, and C<sub>3</sub>-C<sub>8</sub>-cycloalkyl-C<sub>2</sub>-C<sub>18</sub>-alkenyl or the radicals

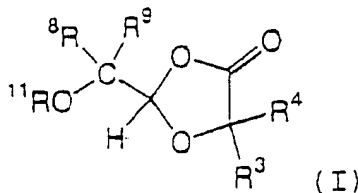
R<sup>8</sup> and R<sup>9</sup> form, together with the carbon to which they are bonded, an unsubstituted or substituted or a heteroatom-containing cycloalkylidene, and m and n are, independently of one another, 0 or 1, and the following applies to the radical

$R^{10}$ : if m is 0 then the radical  $R^{10}$  is selected from the group consisting of substituted or unsubstituted  $C_1$ - $C_{18}$ -alkyl,  $C_2$ - $C_{18}$ -alkenyl or  $C_2$ - $C_{18}$ -alkynyl, substituted or unsubstituted  $C_6$ - $C_{18}$ -aryl,  $C_3$ - $C_{18}$ -heteroaryl, and substituted or unsubstituted silaalkyl or silaaryl, and if m is 1 then the radical  $R^{10}$  is selected from the group consisting of substituted or unsubstituted aryl, substituted or unsubstituted  $C_1$ - $C_{18}$ -alkyl,  $C_2$ - $C_{18}$ -alkenyl, or  $C_2$ - $C_{18}$ -alkynyl.

Where the radicals are substituted radicals, these are preferably substituted by alkyl, alkenyl, alkynyl, aryl, heteroaryl, hydroxyl, alkoxy, carboxylate, alkoxycarbonyl, amino, nitro or halo radicals.

Where the abovementioned radicals contain a heteroatom, it is preferably O, N or S.

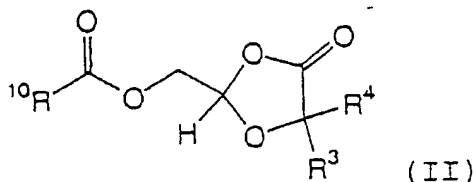
Mixtures of enantiomers of the general formula (I)



where  $R^3$ ,  $R^4$ ,  $R^8$  and  $R^9$  have the meaning mentioned above, and  $R^{11}$  are substituted or unsubstituted, branched or unbranched  $C_1$ -

$C_{18}$ -alkyl,  $C_2$ - $C_{18}$ -alkenyl or  $C_2$ - $C_{18}$ -alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted silaalkyl or silaaryl, or  $R^{11}$  is  $COR^{10}$  where  $R^{10}$  has the meaning mentioned above, are preferably used.

Mixtures of enantiomers of the general formula (II)



where  $R^3$  and  $R^4$  have the meaning mentioned above, and  $R^{10}$  is selected from the group consisting of substituted or unsubstituted aryl, substituted or unsubstituted  $C_1$ - $C_{18}$ -alkyl,  $C_2$ - $C_{18}$ -alkenyl and  $C_2$ - $C_{18}$ -alkynyl, are particularly preferably used.

The nucleophile NuH is preferably an oxygen-containing nucleophile  $OR^5$ .

The oxygen-containing nucleophile is particularly preferably a lower, unbranched alcohol, (e.g. methanol ( $R^5 = CH_3$  or ethanol ( $R^5 = CH_2CH_3$ )) or water ( $R^5 = H$ )).

All enzymes able to cleave an ester linkage are in

terminating the pumping.

The uncleaved, pure enantiomer is preferably isolated by removing the byproducts of the reaction and the solvent.

The free carbonyl compound  $R^1COR^2$  resulting from the cleavage of a 1,3-dioxolan-4-one or 1,3-oxathiolan-5-one ring and the acid derivative  $HXCR^3R^4CONu$  can be removed from the reaction solution by simple physical operations. This preferably takes place by distillation.

It is additionally possible for further breakdown products formed on cleavage of other functional groups in the molecule to be removed easily. This preferably takes place by distillation.

It is preferred for the low-boiling compounds to be removed first by distillation. It has been found, surprisingly, that the alcohol ( $R^1 = H$ ,  $R^2 = CH_2OH$ ) which is a byproduct of the racemate resolution of an ester dioxolanone ( $X = O$ ;  $R^1 = H$ ,  $R^2 = CH_2-O-(CO)-R^{10}$ ) can be removed by simple extraction, preferably with water.

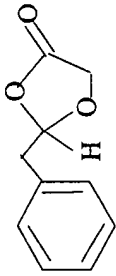
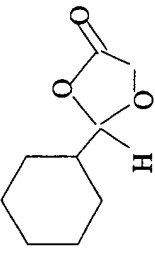
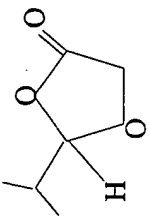

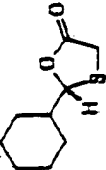
The carbonyl compound resulting from the enzymatic

considered in connection with the accompanying examples. It is to be understood, however, that the examples are designed as an illustration only and not as a definition of the limits of the invention.

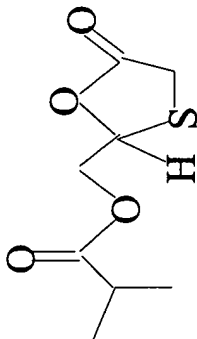
Example 1: (4-oxo-1,3-dioxolan-2-yl)methyl (+)-(R)-  
2-methylpropanoate (batch process)

50.0 g (0.27 mol) of racemic (4-oxo-1,3-dioxolan-2-yl)methyl 2-methylpropanoate ( $X = O$ ;  $R^1 = H$ ;  $R^2 = CH_2-O-(CO)-CH(CH_3)_2$ ;  $R^3, R^4 = H$ ) are dissolved in a mixture of 185 ml of MTBE and 185 ml of methanol ( $Nu = OCH_3$  in a 1 l 4-necked flask. 2.6 g of Novozym® 435 are added to this solution, and the mixture is stirred vigorously.

A polarimeter is connected via a bypass system to the 4-necked flask and is used to follow the progress of the reaction through measurement of the optical rotation of the solution. When the desired enantiopurity (reaction followed by chiral GC) is reached, the reaction is terminated by filtering the reaction mixture to remove undissolved enzymes. The reaction mixture is then concentrated in vacuo. The residue is then taken up in 100 ml of MTBE and washed twice

Substituents in equation 5	Racemate	Product	Selectivity according to Sih*
3 X = O; R <sup>1</sup> = H; R <sup>2</sup> = -CH <sub>2</sub> -C <sub>6</sub> H <sub>5</sub> R <sup>3</sup> , R <sup>4</sup> = H		(+) -2-Methylphenyl-1,3-dioxolan-4-one	11
4 X = O; R <sup>1</sup> = H; R <sup>2</sup> = -C <sub>6</sub> H <sub>11</sub> R <sup>3</sup> , R <sup>4</sup> = H		(+) -2-Cyclohexyl-1,3-dioxolan-4-one	65
5 X = O; R <sup>1</sup> = H; R <sup>2</sup> = -CH(CH <sub>3</sub> ) <sub>2</sub> R <sup>3</sup> , R <sup>4</sup> = H		(+) -2-iso-Propyl-1,3-dioxolan-4-one	14
6 X = O; R <sup>1</sup> = H; R <sup>2</sup> = -C <sub>7</sub> H <sub>15</sub> R <sup>3</sup> , R <sup>4</sup> = H		(+) -2-Heptyl-1,3-dioxolan-4-one	13
7 X = S; R <sup>1</sup> = H; R <sup>2</sup> = -C <sub>6</sub> H <sub>11</sub> R <sup>3</sup> , R <sup>4</sup> = H		(+) -2-Cyclohexyl-1,3-oxathiolan-5-one	65



8	$X = S; R^1 = H; R^2 = -CH_2O(CO)-$ $CH(CH_3)_2$ $R^3, R^4 = H$		(+) - Isobutyryloxy- methyl-1,3-oxathiolan- 5-one	65
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\* Chen, C.-S. et al., J. Am. Chem. Soc. 104, 7294-7299 (1982)